

CLAIMS

We claim:

1. A method for suppressing tumor growth in an individual comprising:
5 administering a target cell-specific adenovirus vector, said vector comprising an
adenoviral gene essential for replication under transcriptional control of a target cell-
specific-transcriptional regulatory element (TRE), and at least one antineoplastic
agent in amounts sufficient to suppress tumor growth, wherein the amount of
adenovirus vector and/or antineoplastic agent administered is less than that known in
10 the art to be effective for suppressing tumor growth when administered alone.

2. The method of claim 1, wherein the antineoplastic agent includes
alkaloids, alkylating agents, antibiotics, antimetabolites, immunomodulators,
nitrosoureas, hormone antagonists/agonists and analogs, or photosensitizing agents.

3. The method of claim 2, wherein alkaloids include docetaxel,
etoposide, irinotecan, paclitaxel, vinblastine, or vincristine.

4. The method of claim 2, wherein alkylating agent includes
cyclophosphamide, estramustine, ifosfamide, carboplatin, cisplatin, dacarbazine, or
thiotepa.

5. The method of claim 2, wherein antibiotics include bleomycins,
doxorubicin, epirubicin, mitomycins, mitoxantrone, or valrubicin.

6. The method of claim 2, wherein antimetabolites include edatrexate,
methotrexate, 5-azacytidine, 5-fluorouracil, or gemcitabine.

7. The method of claim 2, wherein immunomodulators include
interferon-alpha-2a.

8. The method of claim 2 wherein nitrosoureas include carmustine or lomustine.

9. The method of claim 2 wherein hormone antagonists/agonists and analogs include prednisone, taxmoxifen, exemestane, anastrozole, letrozole, goserelin, or leuprolide.

10. The method of claim 2 wherein photosensitizing agents include porfimer sodium.

11. The method of claim 1 wherein said target cell-specific TRE is specific for target cells including bladder, liver, prostate, breast, colorectal or melanoma cells.

12. The method of claim 11 wherein said target cell-specific TRE includes probasin (PB)-TRE; prostate-specific antigen (PSA)-TRE; mucin (*MUC1*)-TRE; α -fetoprotein (AFP)-TRE; *hKLK2*-TRE; tyrosinase-TRE; human uroplakin II-TRE (hUPII); carcinoembryonic antigen (CEA)-TRE; or cell status-specific-TRE.

13. The method of claim 11 wherein said TRE specific for liver cells is an AFP-TRE.

14. The method of claim 11 wherein said TRE specific for prostate cells include PB-TRE; PSA-TRE; and *hKLK2* TRE.

15. The method of claim 11 wherein said TRE specific for breast cells include CEA-TRE and *MUC1*-TRE

16. The method of claim 11 wherein said TRE specific for colorectal cells is a CEA-TRE.

17. The method of claim 11 wherein said TRE specific for melanoma cells is a tyrosinase-TRE.

18. The method of claim 1 wherein said adenoviral gene essential for replication is an early gene.

19. The method of claim 1 wherein said adenoviral gene essential for replication is a late gene.

20. The method of claim 18 wherein said adenoviral gene essential for replication is E1A.

21. The method of claim 18 wherein said adenoviral gene essential for replication is E1B.

22. The method of claim 20 wherein E1A has a mutation in or deletion of its endogenous promoter.

23. The method of claim 21 wherein E1B has a mutation in or deletion of its endogenous promoter.

24. The method of claim 21 wherein E1B has a deletion of the 19-kDa region.

25. The method of claim 1, wherein the adenoviral vector comprises co-transcribed first and second genes under transcriptional control of a target cell-specific TRE wherein the second gene is under translational control of an IRES and wherein at least one of said first and said second genes is an adenovirus gene essential for replication.

26. The method of claim 1, wherein the TRE is specific for prostate cells and the antineoplastic agent includes antimetabolites, alkylating agents, antibiotics or

alkaloids.

27. The method of claim 26, wherein the TRE is specific for prostate cells and the antineoplastic agent includes doxorubicin, mitoxantrone, paclitaxel, docetaxel, etoposide, 5-fluorouracil, estramustine, or cisplatin.

28. The method of claim 27 wherein the TRE specific for prostate cells includes PB-TRE; PSA-TRE; or *hKLK2* TRE.

29. The method of claim 1, wherein the TRE is specific for liver cells and the antineoplastic agent includes antimetabolites, alkylating agents, antibiotics and alkaloids.

30. The method of claim 29, wherein the TRE is specific for liver cells and the antineoplastic agent includes doxorubicin, mitoxantrone, mitomycin C, paclitaxel, 5-azacytidine, gemcitabine, docetaxel, etoposide or cisplatin.

31. The method of claim 30 wherein said TRE is an AFP-TRE.

32. The method of claim 31 wherein said AFP-TRE is SEQ ID NO:___.

33. The method of claim 1, wherein the TRE is specific for bladder cells and the antineoplastic agent includes alkylating agents, antibiotics, immunomodulators, alkaloids, antimetabolites or hormone antagonists/antagonists and analogs.

34. The method of claim 33, wherein the antineoplastic agent includes cisplatin, thiotepa, mitomycin C, interferon alpha-2a, doxorubicin, mitoxantrone, bleomycin, paclitaxel, etoposide, gemcitabine, 5-fluorouracil, vinblastine, ifosfamide, methotrexate, goserelin, leuprolide, valrubicin, gallium nitrate, cyclophosphamide, vincristine, carboplatin, or docetaxel.

35. The method of claim 34 wherein said TRE is a uroplakin-TRE.

36. The method of claim 33 wherein said TRE is a uroplakin- TRE and said antineoplastic agent is doxorubicin.

5

37. The method of claim 1 wherein the TRE is CEA-TRE and the antineoplastic agent includes antibiotics, alkaloids, alkylating agents, antimetabolites and hormonal antagonists/agonists or analogs.

10 38. The method of claim 37, wherein the antineoplastic agent includes doxorubicin, mitoxantrone, epirubicin, mitomycin C, paclitaxel, 5-fluorouracil, thiotepa, goserelin, exemestane, methotrexate, irinotecan, edatrexate, letrozole, leuprolide, cisplatin, tamoxifen, anastrozole, prednisone, docetaxel, cyclophosphamide, or vinblastine.

15

39. The method of claim 1 wherein the TRE is tyrosinase-TRE and the antineoplastic agent includes alkylating agents, alkaloids, nitrosoureas and hormone antagonists/antagonists or analogs.

20

40. The method of claim 39 wherein the antineoplastic agent includes dacarbazine, carmustine, vinblastine, lomustine, tamoxifen, cisplatin, paclitaxel or docetaxel.

25

41. The method of claim 1 wherein a combination of antineoplastic agents is administered.

42. The method of claim 41 wherein said TRE is AFP and said combination includes doxorubicin/cisplatin, doxorubicin/mitomycin C, doxorubicin/mitoxantrone or doxorubicin/paclitaxel.

30

43. The method of claim 41 wherein said TRE includes PSA-TRE, PB-TRE and hKLLK2-TRE and the combination includes estramustine/mitoxantrone,

estramustine/paclitaxel or estramustine/docetaxel.

44. The method of claim 41 wherein the TRE is a uroplakin-TRE and the combination includes M-VAC (methotrexate-
5 vinblastine/doxorubicin/cyclophosphamide), CISCA
(cyclophosphamide/doxorubicin/cisplatin), CMV
(cisplatin/methotrexate/vinblastine), CAP (cyclophosphamide/doxorubicin/cisplatin),
or MVMJ (methotrexate/vinblastine/mitoxantrone/carboplatin).

10 45. The method of claim 41, wherein the TRE is CEA and the
combination includes levamisole/5-fluorouracil, leucovorin/5-fluorouracil, CAF
(cyclophosphamide/doxorubicin/5-fluorouracil), CMF
(cyclophosphamide/methotrexate, 5-fluorouracil), CNF
15 (cyclophosphamide/mitoxantrone/5-fluorouracil), FAC (5-
fluorouracil/doxorubicin/cyclophosphamide), MF (methotrexate/5-
fluorouracil/leucovorin), MV (mitoxantrone/vinblastine), CMFP
(cyclophosphamide/methotrexate/5-fluorouracil/prednisone), or VATH
(vinblastine/doxorubicin/thiotepa/fluoxymesterone).

20 46. The method of claim 41, wherein the TRE is tyrosinase and the
combination includes DBPT (dacarbazine/cisplatin/carmustine/tamoxifen) or VDD
(vinblastine/dacarbazine/cisplatin).

25 47. A method for suppressing tumor growth in an individual comprising:
administering a target cell-specific adenoviral vector, said vector comprising an
adenoviral gene essential for replication under transcriptional control of a target cell-
specific-TRE, and administering an effective amount of an appropriate course of
radiation therapy to the individual wherein wherein the amount of adenovirus vector
and/or radiation administered is less than that known in the art to be effective for
30 suppressing tumor growth when administered alone.

48. The method of claim 47 wherein said radiation includes external and internal radiation.

49. The method of claim 48 wherein said external radiation includes X-rays, gamma rays, alpha particles, beta particles, electrons, photons, neutrons, and other ionizing radiation.

50. The method of claim 48 wherein said internal radiation includes radioactive isotopes.

51. The method of claim 47 wherein said target cell specific TRE is a prostate specific TRE and said radiation is γ -irradiation.

52. A method for suppressing tumor growth in an individual comprising the following steps, in any order:

- a) administering to the individual an effective amount of a target cell-specific adenoviral vector and an effective amount of at least one antineoplastic agent; and
- b) administering an effective amount of an appropriate course of radiation therapy to the individual, wherein the amount of adenovirus vector and/or antineoplastic agent and/or radiation administered will be less than that known in the art to be effective for suppressing tumor growth when administered alone.

53. The method of claim 52 further comprising c) administering to the individual an additional dose of adenoviral/antineoplastic agent or radiation as necessary to suppress tumor growth.

54. The method of claim 53 further comprising a delay between any of steps a), b) and c).

55. A composition comprising a target cell-specific adenoviral vector, said vector comprising an adenoviral gene essential for replication under transcriptional control of a target cell specific-TRE, and at least one antineoplastic

agent.

56. The composition of claim 55 further comprising a suitable pharmaceutical excipient.

5

57. The composition of claim 56 where the pharmaceutical excipient comprises saline solution, buffers, preservative, stabilizers, antiemetics or other adjuvant therapies.

10 58. A kit comprising the composition of claim 55 in an amount effective for suppressing tumor growth in an individual.

11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000